

**PATENT COOPERATION TREATY**  
**PCT**  
**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**  
(PCT Article 36 and Rule 70)

REC'D 31 JAN 2005

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Applicant's or agent's file reference LEIV/P28835PC	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/APEA/416)	
International application No. PCT/GB 03/03612	International filing date (day/month/year) 18.08.2003	Priority date (day/month/year) 16.08.2002
International Patent Classification (IPC) or both national classification and IPC C12N15/11		
Applicant UNIVERSITY OF LEICESTER et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
  
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
  - This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 9 sheets.
  
3. This report contains indications relating to the following items:
  - I  Basis of the opinion
  - II  Priority
  - III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV  Lack of unity of invention
  - V  Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI  Certain documents cited
  - VII  Certain defects in the international application
  - VIII  Certain observations on the international application

Date of submission of the demand 10.03.2004	Date of completion of this report 27.01.2005
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Petri, B Telephone No. +49 89 2399-7356



**INTERNATIONAL PRELIMINARY  
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International application No.

PCT/GB 03/03612

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-70 as originally filed

**Sequence listings part of the description, Pages**

1-6 as originally filed

**Claims, Numbers**

1-56 received on 18.10.2004 with letter of 15.10.2004

**Drawings, Sheets**

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

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5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-20, 56
Inventive step (IS)	Yes: Claims	21-55
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-56
	No: Claims	

2. Citations and explanations

**see separate sheet**

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Reference is made to the following document/s/:

D1: CHAPPELL S A ET AL: "A 9nt segment of a cellular mRNA can function as an internal ribosome entry site (ires) and when present in linked multiple copies greatly enhances ires activity" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 97, no. 4, 15 February 2000 (2000-02-15), pages 1536-1541, XP002202271 ISSN: 0027-8424

Discloses an IRES within the homeodomain mRNA gtx.

D2: BRUZIK JAMES P ET AL: "Enhancer-dependent interaction between 5' and 3' splice sites in trans" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 92, no. 15, July 1995 (1995-07), pages 7056-7059, XP002201267 ISSN: 0027-8424

Discloses enhancer dependent trans splicing and an ESE within exon 4 of dsx.

D3: SKORDIS LEIGH A ET AL: "Bifunctional antisense oligonucleotides provide a trans-acting splicing enhancer that stimulates SMN2 gene expression in patient fibroblasts." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 1 APR 2003, vol. 100, no. 7, 1 April 2003 (2003-04-01), pages 4114-4119, XP002262848 ISSN: 0027-8424

Is the scientific publication of the application.

D4: CARTEGNI LUCA ET AL: "Listening to silence and understanding nonsense: exonic mutations that affect splicing." NATURE REVIEWS: GENETICS. ENGLAND APR 2002, vol. 3, no. 4, April 2002 (2002-04), pages 285-298, XP002262849 ISSN: 1471-0056

**Re Item II**

**Priority**

1. Since the priority document pertaining to the present application is not yet available to the IPEA, this Written Opinion/IPER has been drawn up considering the priority date of 16.0802 as valid. D3 has been published between the priority date and the filing date of the present application. Thus, said document is not considered to constitute prior art in the meaning of rule 64(1)(b) PCT. However, if it turns out that the effective date of the claimed subject-matter is not the priority date then D3 will become relevant to assess whether the present application satisfies the criteria set forth in Article 33(2) and (3) PCT.

**Re Item V & Re Item VIII**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement & Certain observations on the international application**

2. The gist of the instant application is a method for targeting functional RNA-domains such as IRES and ESES to genes by means of bifunctional antisense oligonucleotides.
3. Insofar as claims 1-20, 56 are product claims a mere functional definition is not appropriate. While it may well be that particular exemplified bifunctional constructs may constitute patentable inventions a mere parametrically functional definition in the present case is completely inappropriate.

The claims are broadly directed to nucleic acid molecules comprising a first domain being capable of forming a first specific binding pair with a target sequence of a target RNA species within 100 nucleotides of an RNA processing or translation site and a second domain consisting of a sequence which forms a second specific binding pair with at least one RNA processing or translation factor.

Due to the fact that the target sequence is not specified the target sequence can be any sequence. The fact that the position of the target sequence is defined in relation to an other functional element does not impose any structural limitation upon said target sequence. As a consequence a domain/sequence capable of forming a first specific binding pair with potential any sequence can also be any sequence. As a further consequence any nucleic acid comprising sequences that bind RNA processing or translation factors will fall under the definition of such claims.

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Therefore, the subject-matter proposed in claim 1-20, 56 of the present application cannot be considered as novel (Article 33(2) PCT).

4. The intended use of such sequences, i.e. being actual used as antisense domains for targeting, however can only unfold distinguishing characteristics in the context of a method and/or process claim (i.e. claims 21-55). Said methods and uses appear to involve an inventive step (see however below item 5)
  
5. The question to what extend the method and use-claim actually will be considered to define patentable inventions, will entirely hinge on the question on whether the claimed methods and uses contain all essential technical features in order to put the skilled person in the position to practice the invention over the whole claimed scope. This issue may likewise be seen under on whether the technical problem is solved over the entire scope. These complex issues however need to be the subject of any regional phase. In said context, however it appears worth noting that the worked examples appear to concern splicing factors only. Furthermore it appears as if particular configurations in the constructs were necessary in order to work properly. In absence of any concept fit for generalization it appears as if the claims in their present form impose an undue burden upon the skilled person when working the claimed subject-matter beyond exemplified subject-matter.